

polypeptides, vectors and host cells containing the DNA, and methods of producing the polypeptides using such a host cell, as well as the pharmaceutical compositions. The present invention is also directed to oligonucleotide sequences encoding an antisense sequence of at least a part of an mRNA encoding a polypeptide of the present invention and a pharmaceutical composition containing such oligonucleotide. Also disclosed are antibodies, various methods of use and methods of screening.

The examiner has reconsidered the restriction requirement, deemed it proper and made it final, although she has rejoined the species DNA sequences encoding analogs and derivatives of B1, "but not the species isoforms". This restriction requirement is again respectfully traversed, particularly insofar as the polypeptide claims are concerned.

Applicants previously argued that the PCT Administrative Instructions conclusively establish that polypeptides and DNA that encodes such polypeptides share the same technical feature. The examiner did not find this argument persuasive, stating only "B1 protein is an additional product, wherein the structure of B1 protein is patentably distinct from the structure of a DNA sequence encoding B1 protein." The examiner has not explained why she is ignoring PCT Administrative Instructions, Annex B, Unity of Invention,

Part 2, Examples Concerning Unity of Invention, Example 17, which expressly states with respect to the propriety of restriction between a first claim directed to a DNA sequence and a second claim directed to the protein encoded thereby that expression of the DNA sequence in a host results in production of a protein which is determined by the DNA sequence and, therefore, the protein and the DNA sequence exhibit corresponding special technical features and unity between the two claims is accepted. These Administrative Instructions may not be disregarded by examiners. The policy of the Patent and Trademark Office for cases where unity of invention applies (37 C.F.R. §1.475) is to consider that DNA and the protein encoded thereby share a special technical feature. The examiner's comments may be applicable to restriction requirements under U.S. restriction practice, but not under PCT unity of invention practice. Respectfully, applicants are aware of no authority by which an examiner may disregard PCT Administrative Instructions that are directly on point. Accordingly, at least claims 40-43 should be examined with the elected DNA claims. Similarly, composition claim 22, which includes the polypeptide of claim 40 and a pharmaceutical excipient, should also be examined with the polypeptide and the DNA claims.

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It is noted that the examiner is examining the composition claims in which the active principle is an antisense oligonucleotide. However, applicants inadvertently failed to claim the antisense oligonucleotide *per se*. Accordingly, new claim 51 has now been added directed to such an oligonucleotide. Claim 51 should be examined with the rest of the DNA claims and with the composition claim that includes such an antisense oligonucleotide.

As to the remaining claims, applicant continues to maintain that they share a special technical feature, and it would not be an undue burden for the examiner to examine the rest of them. Reconsideration and withdrawal of the restriction requirement, at least with respect to claims 40-43, 22 and 51, are, therefore, respectfully urged.

The examiner has required a substitute specification because the specification was submitted without an adequate margin on top and holes punched through the specification in order to insert it in Patent Office files have obliterated words which make it difficult to consider the application. The examiner states that a substitute specification will be accepted if applicants submit therewith a marked-up copy which shows the portions of the original specification that are being added and deleted and a statement that the substitute specification includes no new matter and that the substitute

specification includes the same changes as are indicated in the marked-up copy of the original specification showing additions and deletions.

Attached hereto is a substitute specification with an adequate margin on top. No marked-up copy of the specification is being provided as applicants do not know which words have been obliterated. The undersigned hereby states that the attached substitute specification is identical in content to the specification as originally submitted. Since no changes are being made thereto, a marked-up copy is not necessary, nor is a statement that the substitute specification includes no new matter and includes the same changes that are indicated the marked-up copy. Nevertheless, the undersigned hereby states that, in view of the fact that the specification is identical to that as originally submitted, no new matter is present in the substitute specification. Please accept the attached substitute specification in order to continue examination in this case.

Claims 5-8, 11, 23, 24 and 44-48 have been rejected under 35 U.S.C. §112, second paragraph, as being indefinite. The examiner states that they are indefinite because claims 44-47, 23 and 24 are dependent on non-elected claims. This part of the rejection is respectfully traversed.

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It has been explained hereinabove why claims 40-43 and 22 should be examined with the elected claims. Accordingly, it is expected that the claims from which claims 5-8, 11, 23, 24 and 44-48 ultimately depend will no longer be non-elected once this issue is finally decided, either by the examiner or upon petition to the Director. Furthermore, the fact that the claims are dependent on a non-elected claim does not make them indefinite. Until those claims are cancelled, the scope and content of the claim is readily ascertainable and, therefore, 35 U.S.C. §112, second paragraph, is inapplicable. In any event, claim 44 has now been amended to place it in independent form and claim 40 has been amended to depend from claim 44. Accordingly, this part of the rejection has been obviated at least for claim 44. Reconsideration and withdrawal of this part of rejection are respectfully urged.

Claims 23 and 24 are considered indefinite for the use of the language "other pathways".

The present claims have now been amended to delete the term "other pathways", thus obviating this part of the rejection.

The examiner states that claim 24 is indefinite because it is not clear what is "an mRNA sequence encoding of the B1 protein mRNA sequence".

Claim 24 has now been amended in order to correct a clerical error in the last amendment and clarify what was intended. The claim now reads "a mRNA sequence encoding a polypeptide according to claim 40". Thus, the indefiniteness noted by the examiner has now been eliminated.

The examiner states that claims 11 and 44-48 are indefinite for the use of the language "a polypeptide which directly or indirectly potentiates cell death". The examiner states that the rejection could be obviated by deleting the terms "directly" and "indirectly".

All of the present claims have now been amended to delete the term "directly or indirectly", thus obviating this part of the rejection.

Accordingly, reconsideration and withdrawal of the 35 U.S.C. §112, second paragraph, rejection is respectfully urged.

Claims 5-8, 11, 23, 24, 44, 46 and 48 have been rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. The examiner states that the referenced DNA sequence encoding an "analog" of a polypeptide of SEQ ID NO:1 having no more than ten changes or a "derivative" of SEQ ID NO:1, fragment or analog thereof includes nucleotide sequences encoding numerous structural derivatives. The examiner states that although the

specification discloses that the types of changes are routinely done in the art, the specification and the claims do not provide any guidance as to which, or how many original amino acids to be substituted as claimed in item (d) of claim 40, or to which type of substitution besides conservative substitution, or which amino acids could be deleted or inserted so that the claimed polypeptide could function as contemplated. The examiner states that specific, not general, guidance is needed to know which amino acids may be changed without abolishing the function of potentiating cell death. Thus, the examiner states that the disclosure fails to provide a representative number of nucleotide sequences encoding said derivatives or analogs and, thus, applicants were not in possession of the claimed nucleotide sequences encoding said derivatives or analogs. Therefore, only the isolated polynucleotide consisting of SEQ ID NO:2, but not the full breadth of the claims, meets the written description provision of 35 U.S.C. §112, first paragraph. This rejection is respectfully traversed.

First of all, it is noted with appreciation that the examiner has not included claims 45 and 47 in this rejection. Thus, the examiner concedes that, not only have applicants provided written description by means of SEQ ID NO:2, but also

for any DNA which due to the degeneracy of the genetic code encodes a polypeptide in accordance with claim 41.

With respect to the examiner's comment about "derivative" in claim 40(d), the examiner's attention is invited to the definition thereof in the present specification at page 31, lines 12-27 (page 30, lines 13-28, of the substitute specification). The term "derivatives" only involves modification of the side groups of one or more amino acid residues or conjugation to another molecule. The specification further explicitly states at page 31, lines 26 and 27 (page 30, lines 27-28, of the substitute specification):

The term "derivatives" is intended to include only those derivatives that do not change one amino acid to another of the twenty commonly occurring natural amino acids.

Thus, it is improper for the examiner to state that this paragraph of claim 40 opens the claim to other amino acid substitutions and deletions when, as indicated above, the specification explicitly states that no original amino acid is to be substituted insofar as the final clause of claim 40 is concerned. This final clause of claim 40 only covers derivatives that may be prepared from the functional groups that occur as side chains on the residues, or the N- or C-terminal groups, by means known in the art. Accordingly, it

is urged that all of the claims place a maximum of ten amino acid additions, substitutions or deletions as specified in item (b) of claim 44. Furthermore, it should be noted that the term "derivative" no longer appears in any of the rejected claims.

To the extent that the examiner considers even this degree of breadth of the claim to be unsupported by the written description of the specification (which is apparently the case in view of the rejection of claim 46), the examiner's attention is invited to the "Revised Interim Written Description Guidelines Training Materials", which have been published at the PTO website. The present claims are generic to DNA which encodes a polypeptide of SEQ ID NO:1, as well as DNA which encodes analogs thereof in which up to ten amino acids are substituted, added or deleted. SEQ ID NO:2 is a species that is actually reduced to practice and disclosed in the specification. Furthermore, by means of the genetic code, anyone reading the specification is clearly in possession of every nucleotide sequence which encodes the polypeptide of SEQ ID NO:1. In order to determine whether there is written description for the claim genus, it must be determined whether a person of skill in the art would expect substantial variation among species encompassed within the scope of the claims. SEQ ID NO:1 has 540 amino acid residues. Only a

maximum of ten modifications are encompassed by the genus. Thus, even with the maximum number of modification, one will be left with a polypeptide with 98.15% identity to the original 540 amino acids of the polypeptide. A variation of less than 2% is not "substantial variation".

Example 14 of the Training Materials indicates that variants that are at least 95% identical to a specified sequence ID number, and have the required function, comply with the written description requirement as there is not substantial variation, and a single species is sufficient to establish that applicant was in possession of the entire genus. If 95% identity is not substantial variation, then certainly 98.15% identity also would not be considered to be "substantial variation". Section II.A.3.a.(2) of the Guidelines for Examination of Patent Applications under 35 U.S.C. 112, ¶1, "Written Description" Requirement (66 F.R. 1099; 5 January 2001) states:

(2) For each claim drawn to a genus:

The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice (see (1)(a), above), reduction to drawings (see (1)(b), above), or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination

of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus (see (1)(c), above).

Here, relevant identifying characteristics of the whole genus are disclosed, as similarity to very specific structures is required. Functional characteristics are specified in that a polypeptide encoded by the DNA sequence must potentiate cell death. There is a known or disclosed correlation between the function and structure, i.e., structure having at least 98% identity would be expected to have a sufficiently homologous structure to have the same function and assays are disclosed in order to test this.

Thus, by analogy to Example 9 of the Training Materials, the single species here is representative of the genus because all members have at least 98% structural identity with the reference compound and because of the disclosure of an assay for identifying all of the at least 98% identical variants of SEQ ID NO:1 that are capable of the specified activity. Thus, one of ordinary skill in the art would conclude that applicants were in possession of the necessary common attributes possessed by the members of the genus, and the disclosure meets the requirements of 35 U.S.C. §112, first paragraph, as providing adequate written description for the claimed invention. Reconsideration and

withdrawal of this rejection are, therefore, respectfully urged.

*Rebut*  
Claims 5-8, 11, 23, 24, 44, 47 and 48 have been rejected under 35 U.S.C. §112, first paragraph, as containing subject matter that is not supported by the specification in accordance with the written description requirement. The examiner states that these claims are drawn to DNA sequence for a portion of SEQ ID NO:2 encoding a fragment of SEQ ID NO:1, which fragment potentiates cell death. The examiner states that it is not clear from the specification which fragment of B1 protein is responsible for potentiating cell death. The examiner, therefore, concludes that the specification fails to provide sufficient descriptive information, such as definitive structural or functional features of the claimed polynucleotide encoding a fragment of SEQ ID NO:1 which potentiates cell death, and there is no description of the conserved regions that are critical to the structure and function of the claimed fragment. Thus, the examiner states that only SEQ ID NO:2, but not the full breadth of the claims, meet the written description provisions of 35 U.S.C. §112, first paragraph. This rejection is respectfully traversed.

The fragments of claim 44(c) are supported by an enabling disclosure. The specification at page 23 discloses

that such fragments can readily be prepared by preparing DNA sequences encoding the B1 protein in which one or more codons are deleted (see page 23, lines 11-14; page 23, line 3, to page 30, line 3; and page 31, lines 1-11 of the originally filed specification (page 22, lines 22-24; page 23, lines 8-13; and page 30, lines 3-12, of the substitute specification)). While substantial work would be involved, it is routine experimentation to test each sequence in which codons have been deleted from the end to see if they express a polypeptide which potentiates cell death by one of the assays defined in the specification. This is no more work than testing hybridomas to see which ones produce active antibodies. This was found not to involve undue experimentation in In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988). *Wands* states at 1404:

The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed.

See also MPEP §2164.06 and §2164.06(b).

The examiner's comments about specific domains of B1 are not really relevant because all one needs to do to determine which fragments work is to remove residues one by one from either end of the full-length protein. Thus, the

genus of active fragments can be determined without undue experimentation without knowledge of which domains are critical for the desired activity. Accordingly, it is apparent that applicants were in possession of the full genus of such fragments for reasons analogous to those discussed above with respect to the analogs. Reconsideration and withdrawal of this rejection insofar as it relates to the term "fragments" as currently defined in claim 44(c), and particularly in claims 43 and 47, are respectfully urged.

Claims 23 and 24 have been rejected under 35 U.S.C. §112, first paragraph as containing subject matter that is not supported by an enabling disclosure. The examiner states that the use of a pharmaceutical composition is inherent therein, but that the specification is not enabling for such uses.

Claims 22-24 have now been amended to change them from "pharmaceutical compositions" to "compositions". The reference to the intended use of the composition has been removed from the claim. Thus, a pharmaceutical use is not inherent in the language of the present claims. It is not necessary to prove such pharmaceutical uses in order to comply with the enablement requirement of 35 U.S.C. §112. Accordingly, reconsideration and withdrawal of this rejection are, therefore, also respectfully urged.

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Claims 5-8, 11, 23, 24, 44 and 46 have been rejected under 35 U.S.C. §112, first paragraph, because the specification, while being enabling for a DNA sequence of SEQ ID NO:2, does not reasonably provide enablement for a nucleotide sequence encoding a derivative of a polypeptide of SEQ ID NO:1. This part of the rejection is respectfully traversed.

As explained hereinabove, the term "derivative" is defined in the specification as not including any modification of a side chain of an amino acid that changes it from one amino acid to another. Thus, a derivative cannot be encoded by DNA. It is a chemical modification of a side chain after the polypeptide is made. In order to clarify this point, claim 44 has now been rewritten in independent form so as not to include DNA sequences encoding derivatives. Claim 40 has been rewritten so as to depend from claim 44 and to include amino acid sequences encoded by the DNA sequence of claim 44 or a derivative thereof. Accordingly, as none of the DNA claims read on sequences encoding derivatives, this part of the rejection has now been obviated.

To the extent that this rejection would apply to claim 40, the following comments are made in view of the fact that the examiner must examine claim 40 in light of the PCT Administrative Guidelines discussed above. As discussed

above, the term "derivative" does not read on unlimited substitutions of amino acids but only on functionalizations of side chains or end chains, which often occurs when making a polypeptide pharmaceutically acceptable. It would not be expected that such derivativizations would affect the specified properties of the polypeptide, and it would not involve undue experimentation to determine whether any given derivative maintains these properties. Accordingly, reconsideration and withdrawal of this part of the rejection insofar as "derivatives" are concerned, are respectfully urged.

To the extent that the examiner is objecting to the scope of the term "analog" or "fragment", it has already been discussed above that the amount of experimentation necessary to test any given sequence that falls within the scope of the claims is not undue in accordance with the *Wands* factors. The analogs are only broad enough to cover less than 2% differences in the amino acid structure. *Wands* indicates that substantial experimentation may take place, as long as it is not undue experimentation. Because the specification discloses assays, the claims are not exceedingly broad, and the specification has much disclosure as to the types of substitutions and the places of substitutions where one would expect the resulting sequence to be operable. The amount of

experimentation here is not undue. Reconsideration and withdrawal of this part of the rejection are also respectfully urged.

Claims 5-8, 11 and 44-47 have been rejected under 35 U.S.C. §112, first paragraph, because the specification, while being enabling for a DNA sequence of SEQ ID NO:2, does not reasonably provide enablement for a DNA sequence of SEQ ID NO:2 encoding a polypeptide of SEQ ID NO:1. The examiner states that the specification does not enable any person skilled in the art to which it pertains to practice the invention commensurate in scope with these claims. The examiner states that SEQ ID NO:1 is a deduced amino acid sequence from a full-length cDNA clone of SEQ ID NO:2, but that one cannot extrapolate the teaching of the specification to the enablement of the claims because there is no teaching of whether any protein product is actually produced. The examiner states that expression of mRNA, specific for a tissue type, does not dictate nor predict the translation of such mRNA into a polypeptide. Thus, the examiner states that predictability of protein translation is not solely contingent on mRNA expression due to the multitude of homeostatic factors affecting transcription and translation. Thus, the examiner concludes that one would not be able to predict if SEQ ID NO:2 could, in fact, be translated into a polypeptide expression

product, and in view of the above, one would be forced into undue experimentation to practice the claimed invention. This rejection is respectfully traversed.

First of all, the present specification is enabling regardless of whether or not the B1 protein exists in nature. The examples show that the protein encoded by the mRNA that was obtained from cells has the properties specified. It does not matter whether that protein was isolated from nature or made recombinantly. One need not predict protein translation in order for the DNA or protein of the present invention to comply with the enablement requirement. The fact is that applicants clearly have an enabling disclosure for the DNA of SEQ ID NO:2. Furthermore, this DNA has been expressed in recombinant systems to obtain the B1 protein of SEQ ID NO:1. The B1 protein, and analogs and fractions thereof, are tested in the Examples of the present specification and shown to have specified properties. Thus, it is not understood what the examiner's point is about SEQ ID NO:1. The protein has been made and tested for properties, and it is irrelevant whether or not the mRNA encoding it, which was found *in vivo*, makes the polypeptide *in vivo*. All evidence suggests that it does, and the few exceptions to the rule that the examiner cites does not change the general rule that those of ordinary skill in the art would expect expression of B1, at least in some

cells at some time, but, as indicated above, this is irrelevant to enablement of the presently rejected claims. Reconsideration and withdrawal of this rejection are, therefore, respectfully urged.

Claims 5-8, 11, 23, 24, 44 and 48 have been rejected under 35 U.S.C. §112, first paragraph, because the specification, while being enabling for a DNA sequence of SEQ ID NO:2 and a method for producing SEQ ID NO:1 comprising expressing of a vector comprising a DNA sequence encoding SEQ ID NO:1, does not reasonably provide enablement for a DNA sequence encoding a polypeptide which "directly or indirectly" potentiates cell death and a method for producing "any" polypeptide which "directly or indirectly" potentiates cell death. This rejection is respectfully traversed.

First, claim 11 has been amended to delete "directly or indirectly". Secondly, claim 11 is dependent from claim 8, which is ultimately dependent from claim 44. By definition, the only peptide which potentiates cell death which can be produced by the method of claim 11 is a polypeptide in accordance with claim 40. Thus, read as a whole, claim 11 does not read on a method for producing any polypeptide which potentiates cell death. It only reads on a method for producing those polypeptides that potentiate cell death which one can obtain by expressing a host cell of claim 8. The

claim simply does not read on producing proteins whose structure is not the same as a polypeptide of claim 40. The word "any" does not appear in the claim. The method produces a polypeptide. Because of the definition of the host cell according to claim 8, the only polypeptide being produced is one in accordance with claim 40, which, in accordance with the preamble thereof, is one which potentiates cell death. Thus, claim 11 is completely accurate and only reads on producing those polypeptides that one can obtain by growing the host cells of claim 8.

As to the remainder of the rejection, in view of elimination of the term "directly or indirectly", it is believed that this has been obviated. It does not matter how B1 potentiates cell death. The examples show that it does, and this is sufficient, whether it is direct or indirect. Accordingly, reconsideration and withdrawal of this rejection are also respectfully urged.

#4 The examiner states that claims 5-8, 11, 23, 24, 44, 47 and 48 are rejected under 35 U.S.C. §112, first paragraph, because the specification, while being enabling for a DNA sequence of SEQ ID NO:2, does not reasonably provide enablement for a fragment or a portion of a DNA sequence of SEQ ID NO:2 which potentiates cell death. The examiner states that a fragment or a portion could be as little as one or two

nucleotides and that the specification fails to provide sufficient descriptive information, such as definitive structural or functional features of the claimed polynucleotide encoding a fragment of SEQ ID NO:1 that potentiates cell death. Therefore, it would be a burden for one of skill in the art to make and use the claimed invention. This rejection is respectfully traversed.

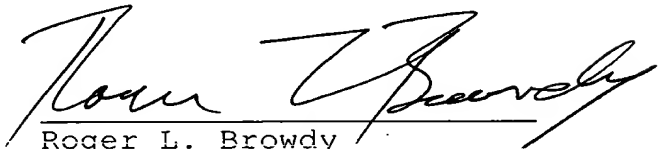
The enablement of fragments of B1 has already been discussed hereinabove. As further indicated above, it does not matter exactly why the polypeptides work, but only that they do. Cell death assays are set forth in the present specification. As indicated above, it does not take undue experimentation to remove one residue at a time from the full-length polypeptide and see which ones retain the disclosed utility. While significant experimentation may be necessary, it is not undue experimentation for the reasons discussed above with respect to the *Wands* factors. No one of ordinary skill would start testing with one residue and then add residues until activity is obtained. Surely, those of ordinary skill would start with the full protein and remove residues at either end until activity is lost. That entails much less experimentation, which would not be "undue". Reconsideration and withdrawal of this rejection are also respectfully urged.

It is noted that the examiner has not made any art rejections and, therefore, the examiner agrees that the present claims define over the prior art of record. It is submitted that all the claims now present in the case fully comply with 35 U.S.C. §112. Reconsideration and allowance are, therefore, earnestly solicited.

Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached page is captioned "Version with markings to show changes made".

Respectfully submitted,

BROWDY AND NEIMARK, P.L.L.C.  
Attorneys for Applicant(s)

By   
Roger L. Browdy  
Registration No. 25,618

RLB:rd  
Telephone No.: (202) 628-5197  
Facsimile No.: (202) 737-3528  
F:\I\in12\Wallach24\Pto\AmendmentC.doc

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Version with Markings to Show Changes Made

Claims 44, 40-42, 11, 22-24, 29, 30, 36 and 37 have been amended as follows:

44 (NewAmended). A DNA sequence encoding a polypeptide ~~in accordance with claim 40~~ which potentiates cell death, said polypeptide consisting of:

(a) a sequence comprising SEQ ID NO:1;

(b) a sequence comprising an analog of (a) having no more than ten changes in the amino acid sequence of (a), each said change being a substitution, deletion or insertion of a single amino acid, which analog potentiates cell death;  
or

(c) a fragment of the sequence of SEQ ID NO:1,  
which fragment potentiates cell death.

40 (NewAmended). A polypeptide which ~~directly or indirectly~~ potentiates cell death, said polypeptide consisting of:

~~\_\_\_\_\_ (a) a sequence comprising SEQ ID NO:1;~~

~~\_\_\_\_\_ (b) a sequence comprising an analog of (a) having no more than ten changes in the amino acid sequence of (a), each said change being a substitution, deletion or insertion of a single amino acid, which analog potentiates cell death;~~

~~\_\_\_\_\_ (c) a fragment of the sequence of SEQ ID NO:1, which fragment potentiates cell death; or~~

non  
ele d.:

~~(d) a derivative of (a), (b) or (c)~~ (an) amino acid  
sequence encoded by a DNA sequence in accordance with claim  
44, or a derivative thereof.

41 (NewAmended). A polypeptide in accordance with  
claim 40, encoding consisting of a sequence comprising SEQ ID  
NO:1.

42 (NewAmended). A polypeptide in accordance with  
claim 40, encoding consisting of a sequence comprising an  
analog of SEQ ID NO:1, having no more than ten changes in the  
amino acid sequence of SEQ ID NO:1, each said change being a  
substitution, deletion or insertion of a single amino acid,  
which analog potentiates cell death.

11 (AmendedTwice-amended). A method for producing a  
polypeptide which ~~directly or indirectly~~ potentiates cell  
death, which comprises growing a transformed host cell  
according to claim 8 under conditions suitable for the  
expression of an expression product, effecting post-  
translational modification of said expression product, as  
necessary, for obtaining said polypeptide, and isolating said  
expressed polypeptide.

22 (AmendedTwice-amended). A ~~pharmaceutical~~  
~~composition for the modulation of the inflammation, cell~~  
~~death, cell survival or other pathways in cells which are~~  
~~modulated directly or indirectly by the B1 protein of SEQ ID~~

~~NO:1~~ comprising a pharmaceutically acceptable excipient and, ~~as active ingredient,~~ at least one polypeptide according to claim 40.

23 (~~Amended~~Twice-amended). A pharmaceutical composition ~~for the modulation of inflammation, cell death, cell survival or other pathways in cells which are modulated directly or indirectly by the B1 protein of SEQ ID NO:1,~~ comprising a pharmaceutically acceptable excipient and, ~~as active ingredient,~~ a recombinant animal virus vector encoding a protein capable of binding a cell surface receptor and encoding said polypeptide according to claim 40.

24 (~~Amended~~Twice-amended). A pharmaceutical composition ~~for modulating the inflammation, cell death, cell survival or other pathways in cells which are modulated directly or indirectly by the B1 protein of SEQ ID NO:1,~~ comprising a pharmaceutically acceptable excipient and, ~~as active ingredient,~~ an oligonucleotide sequence encoding an antisense sequence of at least part of an mRNA sequence encoding ~~of the B1 protein mRNA sequence,~~ a polypeptide according to claim 40.

29 (~~Amended~~Twice-amended). A method of modulating apoptotic processes or programmed cell death processes (cell death pathways) in which the B1 protein of SEQ ID NO:1 is ~~involved directly or indirectly,~~ comprising treating said

cells with one or more polypeptide according to claim 40, wherein said treating of said cells comprises introducing into said cells said one or more polypeptide in a form suitable for intracellular introduction thereof, or introducing into said cells a DNA sequence encoding said one or more polypeptide in the form of a suitable vector carrying said sequence, said vector being capable of effecting the ingestion of said sequence into said cells in a way that said sequence is expressed in said cells.

30 (~~Amended~~Twice-amended). A method of modulating cell survival processes in which the B1 protein of SEQ ID NO:1 is involved ~~directly or indirectly~~ and which include the modulation of cell survival, comprising treating said cells with one or more polypeptide according to claim 40, wherein said treating of cells comprises introducing into said cells said one or more polypeptide in a form suitable for intracellular introduction thereof, or introducing into said cells a DNA sequence encoding said one or more polypeptide in the form of a suitable vector carrying said sequence, said vector being capable of effecting the insertion of said sequence into said cells in a way that said sequence is expressed in said cells.

36 (~~Amended~~Twice-amended). A method for identifying and producing a molecule capable of ~~directly or indirectly~~

modulating the cellular activity modulated or mediated by the B1 protein of SEQ ID NO:1, comprising:

- a) screening for a molecule capable of modulating activities modulated or mediated by said B1 protein;
- b) identifying and characterizing said molecule; and
- c) producing said molecule in substantially isolated and purified form.

37 (~~Amended~~Twice-amended). A method for identifying and producing a molecule capable of ~~directly or indirectly~~ modulating the cellular activity modulated or mediated by a polypeptide according to claim 40, comprising:

- a) screening for a molecule capable of modulating activities modulated or mediated by said polypeptide;
- b) identifying and characterizing said molecule; and
- c) producing said molecule in substantially isolated and purified form.

New claim 51 has been added.